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A retrospective study of insurance coverage status and economic cost of rare diseases in Hainan Province

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Rare diseases present a significant economic burden on patients, families, and healthcare systems worldwide. As the prevalence of these diseases rises in China, data regarding their impact, specifically in Hainan Province, is scarce. Thus, this study aims to evaluate insurance coverage, economic costs, and the factors contributing to the burden of rare diseases in Hainan. We employed a bottom-up approach to analyse the prevalence and economic burden from 2019 to 2023, utilising data from the Hainan Provincial Health Commission Databases. We assessed insurance coverage as well as expenditures related to hospitalisation, diagnostics, medications, surgery, and out-of-pocket costs. Of 4,975 patients diagnosed with 99 distinct rare diseases, 83.01% were insured. From 2019 to 2023, the number of patients increased from 760 to 1,328, while economic costs surged from 34.26 million CNY (US$ 4.89 million) to 64.74 million CNY (US$ 8.86 million). Thalassemia major, one of the most prevalent conditions, generated the highest costs. Hospitalisation expenses accounted for 49.16% of the total costs, with out-of-pocket expenses averaging 17.52%. The findings reveal a significant economic burden associated with rare diseases in Hainan, highlighting the necessity for targeted policy interventions. Furthermore, additional research is needed to refine estimates of this economic burden.

Keywords Rare diseases, Economic cost, Disease burden, Prevalence, Medical insurance

Rare diseases, which affect a small percentage of the population, present significant challenges in terms of diagnosis, treatment, and economic burden. Globally, over 300 million people are estimated to be affected by more than 6,000 identified rare diseases, each impacting fewer than 1 in 2,000 individuals[1,2]. In China, rare diseases are prevalent, and millions of individuals face the difficulties associated with these conditions[3–5]. Despite their prevalence, rare diseases often receive limited attention and resources due to their rarity and the complexity of their diagnosis and treatment. These challenges result in profound economic and social consequences for affected individuals and their families[6–8].

In recent years, the Chinese government has made strides to address the healthcare needs of individuals with rare genetic disorders. Initiatives include the inclusion of orphan drugs in the medical insurance directory, with 106 drugs now available for treating 53 distinct rare diseases. These advancements have improved diagnosis, treatment options, and alleviated some of the patient burden[9–11]. However, challenges remain, such as regional coverage disparities and gaps in the healthcare safety net. These issues highlight the urgent need for a cohesive national strategy to support individuals with rare diseases[9,10]. Studies have highlighted the economic burden rare diseases impose, with high medical expenditures and significant out-of-pocket costs. Policy interventions, such as expanding the inclusion of rare disease drugs in the National Reimbursement Drug List and restructuring insurance coverage, are essential to reduce financial strain on patients[4].

Hainan province, located in southern China, is a tropical island known for its growing population, diverse demographics, and a distinctive healthcare system comprising public and private providers alongside advanced medical infrastructure. Despite these unique characteristics, there exists a paucity of research on the economic implications of rare diseases in Hainan province[12,13]. The lack of pertinent data on the economic repercussions of rare diseases in the province hinders the formulation of targeted healthcare policies and interventions to mitigate this burden. Specifically, precise assessments are needed to understand the economic impact of rare diseases on healthcare utilisation and productivity loss and identify the most prevalent rare diseases affecting the population. Without a comprehensive understanding of the economic implications of rare diseases in Hainan

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province, effective resource allocation, healthcare service prioritisation, and evidence-based policy development to alleviate this burden present significant challenges.

The primary objective of this retrospective study is to assess the economic cost of rare diseases in Hainan Province and identify the most common rare diseases affecting the population over the past 5 years. The study aims to provide a comprehensive understanding of the financial impact on patients, families, and the healthcare system by analysing medical records and insurance data obtained from the Provincial Health Commission database. By examining the economic burden of rare diseases in this region, we hope to provide valuable insights to policymakers and healthcare stakeholders to develop targeted interventions to reduce the economic burden of these diseases.

Methods

Study population

This retrospective study encompassed all patients who received inpatient care at one or more hospitals in Hainan province under the ICD-10 diagnostic codes for rare diseases between January 1, 2019, and December 31, 2023. Additional extracted variables comprised the patients' age at admission, sex, number of hospital admissions, marital status, and occupation.

Data source

The data utilised in this study were obtained from the Hainan Provincial Health Commission Databases, which contain comprehensive information for all provincial residents. This includes hospitalisation records, the number of hospital admissions, insurance coverage status, demographic data, diagnostic tests, medications, out-of-pocket expenses, surgical procedures, and rehabilitation. To ensure compliance with China's stringent data protection regulations, patient data from healthcare providers and insurance companies were anonymised before inclusion in the database. The data were linked using a unique, anonymised patient identifier. All annual claims data for patients with rare diseases, including hospital admissions and insurer spending between 2019 and 2023, were retrieved from the Provincial Health Commission database. Identification of patients with rare diseases was based on the International Classification of Diseases, 10 th edition (ICD-10) diagnosis codes for all discernible rare diseases prevalent in Hainan Province (Supplementary File 3). These diseases were cross-referenced with China's Rare Disease List (First and Second Batches)[14].

Ethics

This retrospective study was conducted in accordance with the Declaration of Helsinki.

The Hainan Provincial Health Commission's Institutional Review Board (IRB) approved the study to ensure compliance with ethical standards.

The Hainan Provincial Health Commission's Institutional Review Board waived informed consent.

Cost assessment

Economic costs were estimated using a bottom-up approach, aggregating individual-level healthcare utilisation data to calculate the total economic costs of rare diseases in Hainan province from a social perspective over a five-year period. This approach assumes constant resource utilisation, supported by studies demonstrating that treatment patterns for chronic and rare diseases remain stable over time[10,15,16]. Consistent resource utilisation models enhance cost assessment accuracy by reducing variability from sporadic care episodes. Due to missing data and inconsistencies in the recording of outpatient visits, the focus was exclusively on inpatient data, specifically on direct medical costs such as hospitalisation, diagnostics, medications, surgery, and rehabilitation.

To analyse the trends in rare disease prevalence, healthcare utilisation, and medication expenses in Hainan, we calculated the annual number of services and treatment costs from 2019 to 2023. Prevalence was estimated by the number of rare disease patients divided by the number of all individuals in the same year. Economic costs included hospitalisation, diagnostic procedures (pathology tests, laboratory tests, imaging), medications (Western medicine, Traditional Chinese Medicine [TCM], antibiotics), out-of-pocket expenses, surgeries, and rehabilitation services. We also assessed the number of patients covered by medical insurance and the types of coverage used each year to ensure a comprehensive understanding of the economic costs and insurance coverage of rare diseases in Hainan Province. Subsequently, we calculated the percentage of rare disease-related service use and costs relative to the overall population studied. Additionally, we estimated the economic cost of rare diseases, with more than 20 cases per rare disease incurred in each year for hospitalisation, diagnostics, medication, out-of-pocket expenses, surgery and rehabilitation. The study results were validated by comparing them with national and international data on the prevalence and economic burden of rare diseases.

Statistical analysis

Data management was performed using Microsoft Excel (Microsoft 365 package version 16.47), and statistical analyses were conducted using SPSS (version 22). Descriptive analyses assessed sociodemographic characteristics, healthcare utilisation, and economic costs. Frequency and percentages were used to summarise count data. Trends were analysed using chi-square tests or ANOVA, and confidence intervals were provided for key estimates. Statistical significance was set at p-values less than 0.05.

Results

Socio-demographic data of rare disease patients

A total of 4975 patients were retrieved from medical records, and 99 different types of rare diseases (RDs) were identified from the 207 RDs documented in China's Rare Disease List. The proportion of men in the total

population was 2701 (54.3%), and women was 2275 (45.7%). Insurance coverage was available to 4,094 patients (83.0%), while 838 (17.0%) remained uninsured.

Table 1 Summarises the annual distribution of patients diagnosed with RDs. The total number of patients increased steadily, with 760 patients in 2019 (15.3%), 782 in 2020 (15.7%), 1,093 in 2021 (22.0%), 1,012 in 2022 (20.3%), and 1,328 in 2023 (26.7%). Notably, the average age at admission decreased from 37.18 years in 2019 to 27.46 years in 2023. The shift in the age distribution of rare disease patients was equally significant, indicating a surge from 16.8% in 2019 to 33.7% in 2023 for individuals below nine years old and from 9.9% in 2019 to 19.2% in 2023 for those aged 10–19. Moreover, the percentage of students diagnosed with rare diseases soared from 10.4% in 2019 to 22.1% in 2023. The proportion of employees diagnosed with RDs decreased from 3.6% in 2019 to 1.7% in 2023. Conversely, the percentage of unemployed individuals diagnosed with RDs significantly increased from 8.7% in 2019 to 11.4% in 2023. The unmarried patients diagnosed with rare diseases also experienced a notable increase, rising from 30.8% in 2019 to 55.5% in 2023. Detailed characterisations of these variables for each year are summarised in Table 1.

	2019	2020	2021	2022	2023	Total
Sex						
Male, n (%)	409 (53.8)	430 (55.0)	597 (54.6)	557 (55.0)	708 (53.3)	2701 (54.3)
Female, n (%)	351 (46.2)	352 (45.0)	496 (45.4)	455 (45.0)	620 (46.7)	2275 (45.7)
Insurance coverage						
Yes, n (%)	636 (83.7)	652 (83.4)	917 (83.9)	798 (78.9)	1092 (82.2)	4095 (83.0)
No, n (%)	124 (16.3)	130 (16.6)	176 (16.1)	171 (16.9)	237 (17.8)	838 (17.0)
Age (Years)						
Average	37.18	36.13	35.40	32.64	27.46	
Below 9, n (%)	128 (16.8)	146 (18.7)	237 (21.7)	266 (26.3)	447 (33.7)	1224 (24.6)
10–19, n (%)	75 (9.9)	103 (13.2)	139 (12.7)	156 (15.4)	255 (19.2)	728 (14.6)
20–29, n (%)	80 (10.5)	62 (7.9)	82 (7.5)	70 (6.9)	75 (5.6)	369 (7.4)
30–39, n (%)	111 (14.6)	108 (13.8)	132 (12.1)	90 (8.9)	105 (7.9)	546 (11.1)
40–49, n (%)	118 (15.5)	109 (13.9)	149 (13.6)	121 (12.0)	132 (9.9)	629 (12.6)
50–59, n (%)	109 (14.3)	103 (13.2)	150 (13.7)	124 (12.3)	127 (9.6)	613 (12.3)
60+, n (%)	139 (18.3)	151 (19.3)	204 (18.7)	185 (18.3)	186 (14.0)	865 (17.4)
Marital status						
Single, n (%)	234 (30.8)	299 (38.2)	427 (39.1)	441 (43.6)	737 (55.5)	2138 (43.6)
Married, n (%)	454 (59.7)	452 (57.8)	577 (52.8)	508 (50.2)	541 (40.7)	2532 (51.6
Widowed, n (%)	8 (1.1)	8 (1.0)	10 (0.9)	13 (1.3)	21 (1.6)	60 (1.2)
Divorced, n (%)	9 (1.2)	3 (0.4)	8 (0.7)	8 (0.8)	12 (0.9)	40 (0.8)
Other, n (%)	34 (4.5)	19 (2.4)	32 (2.9)	32 (3.2)	17 (1.3)	134 (2.8)
Occupation						
Civil servants, n (%)	18 (2.4)	13 (1.7)	13 (1.2)	7 (0.7)	10 (0.8)	61 (1.2)
PTP, n (%)	5 (0.7)	2 (0.3)	4 (0.4)	5 (0.5)	6 (0.5)	22 (0.4)
Employed, n (%)	27 (3.6)	27 (3.5)	41 (3.8)	24 (2.4)	22 (1.7)	141 (2.8)
BM, n (%)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	4 (0.1)
Teachers, n (%)	15 (2.0)	19 (2.4)	18 (1.6)	18 (1.8)	15 (1.1)	85 (1.7)
Farmers, n (%)	140 (18.4)	137 (17.5)	167 (15.3)	106 (10.5)	147 (11.1)	697 (14.0)
Students, n (%)	79 (10.4)	102 (13.0)	166 (15.2)	192 (19.0)	294 (22.1)	833 (16.7)
MP, n (%)	0 (0.0)	2 (0.3)	1 (0.1)	1 (0.1)	0 (0.0)	4 (0.1)
Freelancers, n (%)	20 (2.6)	22 (2.8)	28 (2.6)	13 (1.3)	14 (1.1)	97 (1.9)
Self-employed, n (%)	2 (0.3)	6 (0.8)	1 (0.1)	2 (0.2)	3 (0.2)	14 (0.3)
Unemployed, n (%)	66 (8.7)	71 (9.1)	116 (10.6)	94 (9.3)	152 (11.4)	499 (10.0)
Retired, n (%)	66 (8.7)	59 (7.5)	85 (7.8)	98 (9.7)	110 (8.3)	418 (8.4)
Other, n (%)	321 (42.2)	322 (41.2)	452 (41.4)	450 (44.5)	555 (41.8)	2100 (42.2)
Hospital admission						
< 5 times, n (%)	618 (81.3)	647 (82.7)	911 (83.3)	865 (85.5)	1130 (85.1)	4171 (83.9)
5–10 times, n (%)	52 (6.8)	50 (6.4)	76 (7.0)	79 (7.8)	104 (7.8)	361 (7.2)
10–15 times, n (%)	26 (3.4)	16 (2.0)	40 (3.7)	21 (2.1)	31 (2.3)	134 (2.7)
15–20 times, n (%)	19 (2.5)	13 (1.7)	14 (1.3)	13 (1.3)	14 (1.1)	73 (1.5)
> 20 times, n (%)	45 (5.9)	56 (7.2)	52 (4.8)	34 (3.4)	48 (3.6)	235 (4.7)

Table 1. Rare disease patients socio-demographic data. Notes: PTP: Professional and technical personnel; BM: Business managers; MP: Military personnel.

Furthermore, the study revealed a significant financial burden on patients. An escalation was observed in the number of patients incurring hospitalisation costs exceeding 20,000 CNY (US$ 2,736.80) per admission, rising from 192 patients in 2019 to 343 patients in 2023. Congruently, discernible trends were evidenced in diagnostics, drug costs, and out-of-pocket expenses, as shown in Supplementary File 1, which presents a detailed breakdown of hospitalisation costs, surgery, drugs, rehabilitation, out-of-pocket expenses, and diagnostic tiered expenditures for each year from 2019 to 2023.

Figure 1 depicts the number of patients diagnosed with rare diseases (RDs) over five years, detailing the most diagnosed RDs per year. In 2019, haemophilia was the most diagnosed RD, accounting for 9.6% (73/760) of patients, followed by neuromyelitis optica (NMO) (7.9%, 60/760), thalassemia major (TM) (7.8%, 59/760), growth hormone deficiency (GHD) (7.5%, 57/760), and early-onset Parkinson's disease (6.5%, 49/760). In 2020, haemophilia was again prominent, accounting for 10.5% (82/782) of patients, followed by GHD (10.1%, 79/782), thalassemia major (9.5%, 59/760), NMO (6.8%, 5/782), and systemic sclerosis (MS) and ANCA-associated vasculitis (AAV) (both at 6.0%, 47/782 each). GHD was the highest in 2021, with 11.3% (124/1093) of patients, followed by haemophilia (11.2%, 122/1093), thalassemia major (8.7%, 95/1093), NMO (7.0%, 77/1093), and systemic sclerosis (6.4%, 70/1093). Continuing to 2022, GHD accounted for 11.3% (114/1012) of patients, followed by thalassemia major (9.6%, 97/1012), NMO (7.3%, 74/1012), autoimmune encephalitis (AIE) (6.5%, 66/1012), and haemophilia (6.0%, 61/1012). In 2023, growth hormone deficiency was again prominent at 20.8% (276/1328), followed by thalassemia major (10.5%, 140/1328), pemphigus (7.8%, 104/1328), Myasthenia gravis (MG) (6.3%, 84/1328), and haemophilia (5.7%, 76/1328). Overall, the most diagnosed RDs were GHD, thalassemia major, haemophilia, NMO, pemphigus, and systemic sclerosis, accounting for 13.06%, 9.34%, 8.32%, 6.51%, 5.37%, and 4.42%, respectively (Fig. 1). Notably, the prevalence of rare diseases exhibited a modest increase from 0.15% in 2019 to 0.27% in 2023.

Types of medical insurance coverage

Regarding medical insurance coverage, 3968 patients (79.76%) employed a variety of insurance coverage schemes. Within this cohort, 1521 patients (38.33%) were covered by Urban Residents Basic Medical Insurance (URBMI), 503 patients (12.68%) by Urban Employee Basic Medical Insurance (UEBMI), 393 patients (9.90%) by New Rural Cooperative Medical Insurance (NRCMI), 52 patients (1.31%) by Commercial Health Insurance (CHI), and 51 patients (1.29%) by Poverty Relief Health Insurance (PRHI).

Insurance coverage patterns fluctuated significantly across the years, reflecting broader socioeconomic changes and evolving healthcare policies (Fig. 2C and D). Notably, the percentage of patients with URBMI coverage rose significantly from 20.27% in 2019 to 45.79% in 2023. However, it experienced a slight decline to

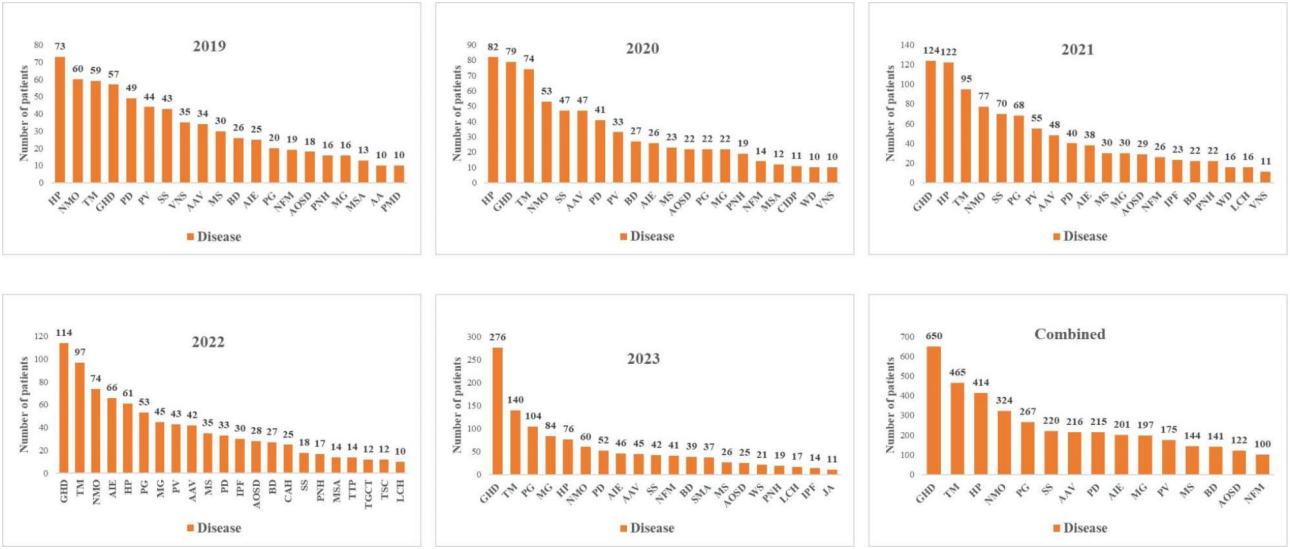

Fig. 1. The most diagnosed rare diseases in each year. The figure shows the number of patients diagnosed with rare diseases for 2019, 2020, 2021, 2022 and 2023, respectively, and the overall most diagnosed rare diseases during the 5-year period. **Notes**: AA: Aplastic anaemia; AAV: ANCA-associated vasculitis; AIE: Autoimmune encephalitis; AOSD: Adult-onset Still disease; BD: Behcet's disease; CAH: Congenital adrenal hyperplasia; CIDP: Chronic inflammatory demyelinating polyneuropathy; GHD: Growth hormone deficiency; HP: Haemophilia; IPF: Idiopathic pulmonary fibrosis; JA: Juvenile arthritis; LCH: Langerhans cell histiocytosis; MG: Myasthenia gravis; MS: Multiple sclerosis; MSA: Multiple system atrophy; NFM: Neurofibromatosis (Non-malignant); NMO: Neuromyelitis optica; PD: Early-onset Parkinson's disease; PG: Pemphigus; PMD: Progressive muscular dystrophy; PNH: Paroxysmal nocturnal haemoglobinuria; PV: Polycythemia vera; SMA: Spinal muscular atrophy; SS: Systemic sclerosis; TGCT: Tenosynovial giant cell tumour; TM: Thalassemia major; TSC: Tuberous sclerosis; TTP: Thrombotic thrombocytopenic purpura; VNS: Villonodular synovitis; WD: Wilson's disease; WS: West syndrome.

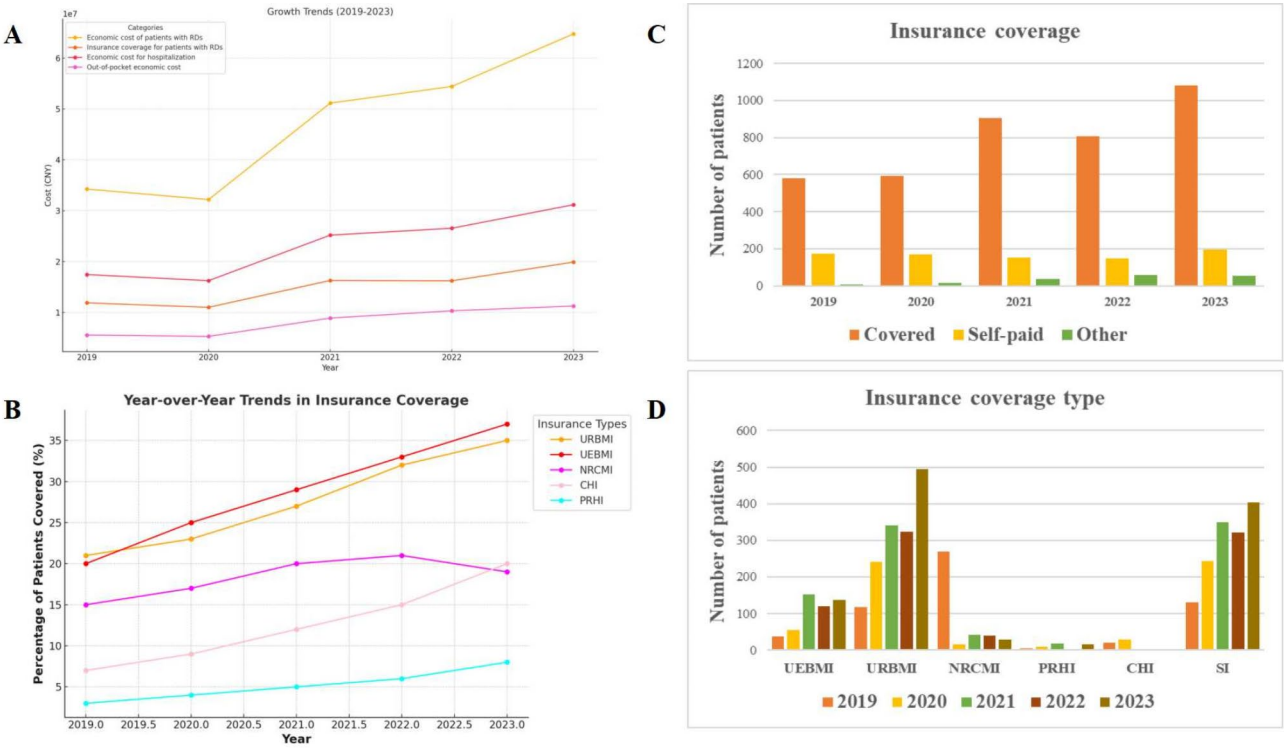

Fig. 2. Medical insurance coverage and growth trends (A) The growth trends of the annual economic costs for different categories (total costs, insurance coverage, hospitalisation costs, and out-of-pocket costs) from 2019 to 2023 (B) The yearly trends for URBMI, UEBMI, NRCMI, CHI, PRHI from 2019 to 2023. Each line represents a category, showcasing its cost trajectory over the years (C) The number of patients covered by medical insurance (D) The types of medical insurance coverage scheme in each year **Notes**: URBMI: Urban residents basic medical insurance; UEBMI: Urban employees basic medical insurance; NRCMI: New rural cooperative medical insurance; CHI: Commercial health insurance; PRHI: Poverty relief health insurance; SI: Other social insurance.

37.79% in 2021. Similarly, the proportion of patients with UEBMI coverage increased steadily, starting at 6.53% in 2019, rising to 16.80% in 2021, and eventually stabilising at 14.89% in 2022. In contrast, the percentage of patients with NRCMI coverage significantly declined, dropping from 46.39% in 2019 to just 2.59% in 2023. Meanwhile, those with CHI coverage peaked at 4.88% in 2021 but fell sharply to 0.09% in 2023. A slight increase was observed in PRHI coverage over the years, which peaked at 2.10% in 2021. Figure 2B illustrates a year-over-year comparative analysis of insurance coverage patterns during the study period. These shifts demonstrate a clear trend towards urban-oriented insurance schemes, with a corresponding decline in rural-focused programs, reflecting evolving healthcare policies and socioeconomic dynamics.

Economic costs of rare diseases in Hainan Province

The economic expenses associated with rare diseases in Hainan Province are delineated in Table 2, presenting the financial burdens shouldered by patients diagnosed with rare diseases over a five-year period. The aggregated annual economic cost increased significantly, from 34,257,363.77 CNY [US$ 4,687,780.70] (95% CI: 31,757,363.77–36,757,363.77 CNY) in 2019 to 64,742,511.28 CNY [US$ 8,859,370.98] (95% CI: 61,242,511.28–68,242,511.28 CNY) in 2023, representing a cumulative growth rate of 88.99% (equivalent to 22.25% per year). Furthermore, the total cost of hospitalisation surged from 17,456,089.03 CNY [US$ 2,388,692.77] (95% CI: 15,956,089.03–18,956,089.03 CNY) in 2019 to 31,178,522.25 CNY [US$ 4,266,471.75] (95% CI: 28,678,522.25–33,678,522.25 CNY) in 2023, reflecting a growth rate of 78.61% (equivalent to 19.65% per year). Similarly, total out-of-pocket expenses grew sharply from 5,562,110.94 CNY [US$ 761,119.75] (95% CI: 5,000,000.00–6,124,221.88 CNY) in 2019 to 11,270,641.84 CNY [US$ 1,542,275.63] (95% CI: 10,120,000.00–12,421,000.00 CNY) in 2023, with an annual growth rate of 102.63% (or 25.66% per annum). Diagnostics costs increased from 3,731,245.23 CNY [US$ 510,583.93] (95% CI: 3,612,000.00–3,850,000.00 CNY) in 2019 to 6,680,445.02 CNY [US$ 914,152.69] (95% CI: 6,512,000.00–6,849,000.00 CNY) in 2023, accounting for 11.13% of total expenses; drugs costs increased from 7,074,007.08 CNY [US$ 968,007.76] (95% CI: 6,812,000.00–7,336,000.00 CNY) in 2019 to 14,974,056.70 CNY [US$ 2,049,051.25] (95% CI: 14,612,000.00–15,336,000.00 CNY) in 2023. Growth trends for economic costs, insurance coverage, hospitalisation and out-of-pocket are shown in Fig. 2A. Surgery and rehabilitation expenses followed a similar upward trend, as detailed in Table 2. An analysis of variance (ANOVA) was conducted to evaluate year-over-year fluctuations in costs, revealing statistically significant increases across various categories. The results indicated significant changes in total costs ($F = 27.8$, $p < 0.01$),

Year	2019	2020	2021	2022	2023	Growth rate (2019-2023)	Annual growth rate
Economic cost of patients with RDs	46,87,780.70	44,05,395.42	69,98,500.35	74,46,086.03	88,59,370.98	88.99%	22.25%
Insurance coverage for patients with RDs	16,27,573.02	15,07,315.47	22,29,854.76	22,20,812.69	27,24,196.10	67.38%	16.84%
Economic cost for hospitalisation	23,88,692.77	22,23,529.66	34,47,930.84	36,34,455.45	42,66,471.75	78.61%	19.65%
Out-of pocket economic cost	7,61,119.75	7,25,503.61	12,18,076.08	14,13,642.77	15,42,275.63	102.63%	25.66%
Economic cost for diagnostics	5,10,583.93	5,74,549.77	8,18,139.63	7,87,675.62	9,14,152.69	79.04%	19.76%
Economic cost for pathology tests	12,335.73	17,596.67	27,861.49	20,892.07	23,932.26	94.01%	23.50%
Economic cost for labolatory tests	359.372.44	4,23,802.91	5,81,739.64	5,48,050.33	6,66,221.69	85.38%	21.35%
Economic cost for Imaging	1,38,875.76	1,33,050.18	2,08,538.51	2,18,733.22	2,23,998.75	61.29%	15.32%
Economic cost for drugs	9,68,007.76	8,28,681.47	14,22,866.26	15,41,882.10	20,49,051.25	111.68%	27.92%
Economic cost for TCM	23,685.04	28,858.13	58,548.07	59,041.17	41,853.23	76.71%	19.18%
Economic cost for Western medicine	8,24,766.23	7,01,909.47	12,29,705.78	13,37,465.01	18,02,597.62	118.56%	29.64%
Economic cost for antibiotics	1,19,556.49	97,913.86	1,34,612.42	1,45,375.92	2,04,600.39	71.13%	17.78%
Economic cost for surgery	50,924.47	42,032.09	72,201.91	55,520.97	72,834.00	43.02%	10.76%
Economic cost for rehabilitation	8,452.01	11,098.81	19,285.62	12,909.12	14,585.67	72.57%	18.14%
Rate of insurance coverage for patients with RDs	34.72%	34.22%	31.86%	29.83%	30.75%	-3.97%	-0.99%
Rate of economic cost for hostipalisation	50.96%	50.47%	49.27%	48.81%	48.16%	-2.80%	-0.70%
Rate of economic cost for out-of-pocket	16.24%	16.47%	17.40%	18.99%	17.41%	1.17%	0.29%
Rate of economic cost for diagnostics	10.89%	13.04%	11.69%	10.58%	10.32%	-0.57%	-0.14%
Rate of economic cost for pathology tests	0.26%	0.40%	0.40%	0.28%	0.27%	0.01%	0.00%
Rate of economic cost for laboratory tests	7.67%	9.62%	8.31%	7.36%	7.52%	-0.15%	-0.04%
Rate of economic cost for imaging	2.96%	3.02%	2.98%	2.94%	2.53%	-0.43%	-0.11%
Rate of economic cost for drugs	20.65%	18.81%	20.33%	20.71%	23.13%	2.48%	0.62%
Rate of economic cost for TCM	0.51%	0.66%	0.84%	0.79%	0.47%	-0.04%	-0.01%
Rate of economic cost for Western medicine	17.59%	15.93%	17.57%	17.96%	20.35%	2.76%	0.69%
Rate of economic cost for antibiotics	2.55%	2.22%	1.92%%	1.95%	2.31%	-0.24%	-0.06%
Rate of economic cost for surgery	1.09%	0.95%	1.03%	0.75%	0.80%	-0.29%	-0.07%
Rate of economic cost for rehabilitation	0.18%	0.25%	0.28%	0.17%	0.16%	-0.02%	-0.01%
Mean economic cost for patients with RDs	6,172.63	5,635.55	6,504.77	7,420.55	6,703.95	8.61%	2.15%
Mean insurance coverage for patients with RDs	2,141.54	1,927.51	2,040.12	2,194.48	2,051.35	-4.21%	-1.05%
Mean economic cost for hospitalisations	3,143.02	2,843.39	3,154.56	3,591.36	3,212.70	2.22%	0.55%
Mean economic cost for out-of-pocket	1,005.44	928.94	1,171.23	1,415.06	1,161.35	15.51%	3.88%
Mean economic cost for diagnostics	671.82	734.83	761.16	791.04	696.85	3.72%	0.93%
Mean economic cost for pathology tests	16.23	22.61	27.75	21.95	18.83	16.01%	4.00%
Mean economic cost for laboratory tests	472.86	542.08	538.15	549.70	506.63	7.14%	1.79%
Mean economic cost for imaging	182.73	170.14	195.26	219.39	171.38	-6.21%	-1.55%
Mean economic cost for drugs	1,274.19	1,059.93	1,332.78	1,551.40	1,564.78	22.81%	5.70%
Mean economic cost for TCM	31.24	37.14	60.3	61.95	32.64	4.48%	1.12%
Mean economic cost for Western medicine	1,085.22	897.58	1,136.51	1,334.80	1,368.72	26.12%	6.53%
Mean economic cost for antibiotics	157.73	125.21	135.97	154.66	163.42	3.61%	0.90%
Mean economic cost for surgery	67.01	54.17	66.06	57.95	56.46	-15.74%	-3.93%
Mean economic cost for rehabilitation	11.15	14.28	18.98	13.73	11.81	5.92%	1.48%

Table 2. Annual estimated economic cost for patients with rare diseases in Hainan (US$). Notes: Percentage of economic cost= economic cost for each category/total economic cost*100. Average economic cost= economic cost for patients with rare diseases/number of patients with rare diseases. Growth rate= (the value in 2023-the value in 2019)/the value in 2019. RDs: Rare diseases; TCM: Traditional Chinese medicine; US$: Unites States Dollars (Bank of China exchange rate: US$ 1=7.3078 Chinese yuan [CNY], as of 2025.02.07).

hospitalisation costs ($F = 19.6$, $p < 0.01$), out-of-pocket expenses ($p = 0.02$), surgical costs ($F = 9.7$, $p < 0.01$), rehabilitation costs ($p = 0.03$), and drug expenses ($F = 12.3$, $p < 0.01$) over the observed time period. Conversely, no significant changes were noted in diagnostic costs, which exhibited a nonsignificant trend over time ($p = 0.09$) despite the overall increase in total costs observed during the analysis.

The average total cost per patient over the 5-year timeframe amounted to 237,046.30 CNY (US$ 32,437.44), with 75,672.35 CNY (US$ 10,355.01) being insured, constituting 31.92% of the total mean cost. The average out-of-pocket expenditure was 41,523.07 CNY (US$ 5,682.02), representing 17.52% of the total annual mean cost; the average out-of-pocket expenditure was highest in 2022, constituting 19.07%. The average cost for hospitalisation was 116,523.05 CNY (US$ 15,945.02), which was the highest in 2022 (26,244.93 CNY [US$ 3,591.36]). Diagnostics was 26,715.10 CNY (US$ 3,655.70), which was the highest in 2022 (5,780.73 CNY [US$

791.04]). However, the stratification of diagnostic modalities showed that the cost of pathology examinations peaked in 2021, while expenses for laboratory tests and imaging were highest in 2022 (Supplementary file 2 A). A similar pattern was observed for rehabilitation costs (511.27 CNY [US$ 69.96]), which peaked in 2021, and surgery costs (2,204.36 CNY [US$ 301.64]), which were highest in 2019. The average drug cost per patient saw a significant increase from 9,311.54 CNY [US$ 1,274.19] (20.64%) in 2019 to 11,435.10 CNY [US$ 1,564.78] (23.34%) in 2023 (Table 2). Among these expenses, the utilisation of Western medicine followed a comparable trajectory, surging from 7,930.56 CNY [US$ 1,085.22] (17.58%) in 2019 to 10,002.29 CNY [US$ 1,368.71] (20.42%) in 2023, with a marginal decrease evident in 2020 (6,559.35 CNY [US$ 897.58], 15.93%) per patient. The average costs associated with Traditional Chinese Medicine (TCM) showed an increase from 228.35 CNY [US$ 31.25] (0.51%) in 2019 to 452.74 CNY [US$ 61.95] (0.83%) in 2022 but then decreased to 238.58 CNY [US$ 32.65] (0.43%) in 2023. Additionally, the cost of antibiotics rose from 1,152.63 CNY [US$ 157.73] (2.56%) in 2019 to 1,194.23 CNY [US$ 163.42] (2.44%) in 2023 (Supplementary file 2B).

Hospitalisation accounted for 49.16% of the total average medical expenses over the 5-year period, while drug costs comprised 20.91%. Diagnostics, surgery, and rehabilitation accounted for 11.27%, 0.93%, and 0.22%, respectively. The highest total annual mean cost was in 2022. Notably, there was a decreasing trend in insurance coverage over the 5-year period from 34.69% in 2019 to 30.60% in 2023, accompanied by a slight increase in out-of-pocket expenditures from 16.29% in 2019 to 17.32% in 2023.

Selected individual rare disease economic cost

The economic burden of selected rare diseases (RDs) with more than 20 cases per year is summarised in Fig. 3. In 2019, the total economic cost amounted to 26,629,537.23 CNY (US$ 3,643,988.24), followed by 22,966,762.63 CNY (US$ 3,142,773.83) in 2020, and substantial increases in 2021, 2022, and 2023, with costs of 41,061,394.61 CNY (US$ 5,618,844.88), 41,405,766.60 CNY (US$ 5,665,968.77), and 55,186,430.20 CNY (US$ 7,551,716.00), respectively. The insured amount accounted for 33.81%, 33.92%, 32.81%, 23.85%, and 30.79% of the total cost in the respective years. Regarding specific diseases, the annual cost of thalassemia major (TM) was highest in 2019 (5,564,397.04 CNY [US$ 761,432.58]) and 2020 (3,968,525.00 CNY [US$ 543,053.31]), accounting for 20.90% and 17.28% of the total cost, respectively, while haemophilia registered its highest cost in 2021 (5,746,118.61 CNY [US$ 786,299.38], 13.99%). Autoimmune encephalitis (AIE) showed the highest cost in 2022 (9,109,115.91 CNY [US$ 1,246,492.23], 22.00%), and in 2023, GHD had the highest cost (14,737,445.68 CNY [US$ 2,016,673.37], 26.70%), as illustrated in Fig. 3.

Detailed analyses revealed significant variations in economic costs among different rare diseases. For example, the total annual cost of Growth Hormone Deficiency (GHD) increased dramatically from 471,904.10 CNY [US$ 64,575.40] (95% CI: 450,000–490,000 CNY) in 2019 to 14,737,445.68 CNY [US$ 2,016,673.37] (95% CI: 14,200,000–15,300,000 CNY) in 2023. The ANOVA analysis revealed a significant cost difference over the 5-year timeframe ($F = 15.4$, $p < 0.01$). Similarly, the costs associated with thalassemia major (TM) remained consistently high, rising from 5,564,397.04 CNY [US$ 761,432.58] (95% CI: 5,300,000–5,800,000 CNY) in

Fig. 3. The economic costs of most common rare diseases The figure shows the economic costs of each rare disease for 2019, 2020, 2021, 2022, and 2023, respectively; and annual total economic costs and the amount insured per annum **Notes**: AAV: ANCA-associated vasculitis; AIE: Autoimmune encephalitis; AOSD: Adult-onset Still disease; BD: Behcet's disease; CAH: Congenital adrenal hyperplasia; GHD: Growth hormone deficiency; HP: Haemophilia; IPF: Idiopathic pulmonary fibrosis; MG: Myasthenia gravis; MS: Multiple sclerosis; MSA: Multiple system atrophy; NFM: Neurofibromatosis; NMO: Neuromyelitis optica; PD: Early-onset Parkinson's disease; PG: Pemphigus; PNH: Paroxysmal nocturnal haemoglobinuria; PV: Polycythemia vera; SMA: Spinal muscular atrophy; SS: Systemic sclerosis; TM: Thalassemia major; WS: West syndrome (Bank of China exchange rate: US$ 1 = 7.3078 Chinese yuan [CNY], as of 2025.02.07).

2019 to 7,588,778.68 CNY [US$ 1,038,449.15] (95% CI: 7,200,000–8,000,000 CNY) in 2023. The costs peaked at 9,109,115.91 CNY [US$ 1,246,492.23] (95% CI: 8,700,000–9,500,000 CNY) in 2022, reflecting its complex diagnostic process and intensive treatments, before declining to 1,482,417.19 CNY [US$ 202,854.10] (95% CI: 1,400,000–1,600,000 CNY) in 2023, with notable cost differences throughout the 5 years ($p < 0.01$).

The total annual cost of haemophilia was 4,203,695.93 CNY [US$ 575,234.12] (95% CI: 4,000,000–4,400,000 CNY) in 2019. It peaked at 5,746,118.61 CNY [US$ 786,299.38] (95% CI: 5,500,000–6,000,000 CNY) in 2021 before stabilising at 3,386,730.10 CNY [US$ 463,440.45] (95% CI: 3,200,000–3,600,000 CNY) in 2023 ($F = 13.8$, $p < 0.01$). Furthermore, myasthenia Gravis (MG) demonstrated a consistent increase in total costs, reaching 3,802,141.92 CNY [US$ 520,285.44] (95% CI: 3,600,000–4,000,000 CNY) in 2023, up from 656,497.89 CNY [US$ 89,835.23] (95% CI: 620,000–680,000 CNY) in 2020. The ANOVA analysis revealed substantial cost differences over the study period ($F = 11.5$, $p < 0.01$). Subsequently, the costs related to pemphigus (PG) rose from 387,950.66 CNY [US$ 53,087.20] (95% CI: 370,000–410,000 CNY) in 2019 to 4,594,165.70 CNY [US$ 628,666.04] (95% CI: 4,300,000–4,800,000 CNY) in 2023 (Fig. 3), which showed significant cost variations over the 5-year period ($p < 0.01$).

Overall, the total mean economic cost amounted to 3,559,268.46 CNY (US$ 487,050.61), of which 1,079,891.34 CNY (US$ 147,772.43) was insured, representing 30.34% of the total mean economic expenditure. Over the 5-year period, the mean health expenditure for patients with RDs increased from 630,015.38 CNY (US$ 86,211.36) in 2019 to 783,895.81 CNY (US$ 107,268.37) in 2023. The highest mean cost was incurred in 2021, amounting to 806,644.26 CNY [US$ 110,381.27] (22.66%). The percentage of the insured decreased from 32.62% in 2019 to 24.42% in 2022, with a slight increment to 31.12% in 2023. Compared to annual economic costs, the total mean cost of AIE was highest in 2019, 2020, 2021, and 2022, accounting for 20.48%, 18.92%, 16.35%, and 17.78%, respectively. In 2023, neurofibromatosis (NFM) had the highest mean cost, reaching 10.16%. The average drug expenditure showed an increasing trend, which increased from 128,122.62 CNY (US$ 17,532.31) in 2019 to 178,540.19 CNY (US$ 24,431.46) in 2023, as detailed in Supplementary File 2D. The average costs for hospitalisation, out-of-pocket expenses, diagnostics, drugs, surgery, and rehabilitation for each year are outlined in Supplementary File 2D, capturing the incremental health expenditure across these categories. The average cost and amount insured in each year are depicted in Supplementary File 2 C.

The prevalence for a range of rare diseases, including growth hormone deficiency (GHD), thalassemia major (TM), haemophilia, neuromyelitis optica (NMO), pemphigus, ANCA-associated vasculitis (AAV), early-onset Parkinson's disease (PD), AIE, multiple sclerosis (MS), and Behcet disease (BD), is illustrated in Table 3. The

Year	2019	2020	2021	2022	2023	Growth rate (2019-2023)	Annual growth rate
Number of RD patients	760	782	1093	1012	1328	74.74%	18.68%
Provincial number of inpatients	12,89,357	11,61,076	12,81,885	12,24,062	14,63,382	13.50%	3.37%
Prevalence of RD (per 10,000 people)	5.89%	6.74%	8.53%	8.27%	9.07%	53.96%	13.49%
Number of patients with GHD	57	79	124	114	176	208.77%	52.19%
Prevalence of GHD (per 10,000 people)	0.44%	0.68%	0.97%	0.93%	1.20%	172.05%	43.01%
Number of patients with TM	59	74	95	97	140	137.29%	34.32%
Prevalence of TM (per 10,000 people)	0.46%	0.64%	0.74%	0.79%	0.96%	109.07%	27.27%
Number of patients with HP	73	82	122	61	76	4.11%	1.03%
Prevalence of HP (per 10,000 people)	0.57%	0.71%	0.95%	0.50%	0.52%	-8.27%	-2.07%
Number of patients with NMO	60	53	77	74	60	0.00%	0.00%
Prevalence of NMO (per 10,000 people)	0.47%	0.46%	0.60%	0.60%	0.41%	-11.89%	-2.97%
Number of patients with PG	20	22	68	53	104	420.00%	105.00%
Prevalence of PG (per 10,000 people)	0.16%	0.19%	0.53%	0.43%	0.71%	358.16%	89.54%
Number of patients with AAV	34	47	48	42	45	32.35%	8.09%
Prevalence of AAV (per 10,000 people)	0.26%	0.40%	0.37%	0.34%	0.31%	16.61%	4.15%
Number of patients with PD	49	41	40	33	52	6.12%	1.53%
Prevalence of PD (per 10,000 people)	0.38%	0.35%	0.31%	0.27%	0.36%	-6.50%	-1.62%
Number of patients with AIE	25	26	38	66	46	84.00%	21.00%
Prevalence of AIE (per 10,000 people)	0.19%	0.22%	0.30%	0.54%	0.31%	62.12%	15.53%
Number of patients with MS	30	23	30	35	26	-13.33%	-3.33%
Prevalence of MS (per 10,000 people)	0.23%	0.20%	0.23%	0.29%	0.18%	-23.64%	-5.91%
Number of patients with BD	26	27	22	27	39	50.00%	12.50%
Prevalence of BD (per 10,000 people)	0.20%	0.23%	0.17%	0.22%	0.27%	32.16%	8.04%

Table 3. Annual prevalence of rare diseases in Hainan Province Notes: Prevalence of all rare diseases (per 10,000 people) = number of patients with all rare diseases/number of people in the same year*10,000. Growth rate= (the value in 2023-the value in 2019)/the value in 2019. RDs: Rare diseases; GHD: Growth hormone deficiency; TM: Thalassemia major; HP: Haemophilia; NMO: Neuromyelitis optica; BD: Behcet disease; AAV: ANCA-associated vasculitis; PG: Pemphigus; PD: Early-onset Parkinson's disease; AIE: Autoimmune encephalitis; MS: Multiple sclerosis.

Year	2019	2020	2021	2022	2023	Growth rate (2019-2023)	Annual growth rate
Economic cost of patients with RDs	30,11,197.55	26,79,902.03	41,14,781.49	49,42,089.98	58,60,875.76	94.64%	23.66%
Economic cost of patients with GHD	64,575.40	1,47,739.69	2,44,343.49	1,25,393.32	20,16,673.37	3022.97%%	755.74%
Economic cost of patients with TM	7,61,432.58	5,43,053.31	6,10,589.70	9,73,038.00	10,38,449.12	36.38%%	9.10%
Economic cost of patients with HP	5,75,234.12	3,12,885.88	7,86,299.38	7,54,272.27	4,63,440.52	-19.43%	-4.86%
Economic cost of patients with NMO	3,13,892.44	3,83,089.78	6,72,887.78	6,73,117.44	2,48,339.25	-20.88%	-5.22%
Economic cost of patients with PG	53,087.20	46,275.19	2,49,779.93	1,80,227.75	6,28,666.04	1084.21%	271.05%
Economic cost of patients with AAV	2,63,382.46	4,06,859.96	4,19,308.81	3,96,908.26	3,75,782.29	42.68%	10.67%
Economic cost of patients with PD	2,63,821.16	1,60,646.92	1,86,486.17	2,68,279.20	5,16,867.61	95.92%	23.98%
Economic cost of patients with AIE	4,49,230.65	3,78,805.76	6,72,999.37	12,46,492.23	2,02,854.10	-54.84%	-13.71%
Economic cost of patients with MS	1,33,491.17	1,36,595.63	1,85,801.80	1,70,138.57	2,38,138.06	78.39%	19.60%
Economic cost of patients with BD	1,33,050.37	1,63,949.90	86,285.07	1,54,222.95	1,31,665.39	-1.04%	-0.26%
Rate of economic cost for patients with GHD	2.14%	5.51%	5.94%	2.54%	34.41%	32.27%	8.07%
Rate of economic cost for patients with TM	25.29%	20.26%	14.84%	19.69%	17.72%	-7.57%	-1.89%
Rate of economic cost for patients with HP	19.10%	11.68%	19.11%	15.26%	7.91%	-11.19%	-2.80%
Rate of economic cost for patients with NMO	10.42%	14.29%	16.35%	13.62%	4.42%	-6.00%	-1.55%
Rate of economic cost for patients with PG	1.76%	1.73%	6.07%	3.65%	10.73%	8.97%	2.24%
Rate of economic cost for patients with AAV	8.75%	15.18%	10.19%	8.03%	6.41%	-2.34%	-0.58%
Rate of economic cost for patients with PD	8.76%	5.99%	4.53%	5.43%	8.82%	0.06%	0.01%
Rate of economic cost for patients with AIE	14.92%	14.14%	16.36%	25.22%	3.46%	-11.46%	-2.86%
Rate of economic cost for patients with MS	4.43%	5.10%	4.52%	3.44%	4.06%	-0.37%	-0.09%
Rate of economic cost for patients with BD	4.42%	6.12%	2.10%	3.12%	2.25%	-2.17%	-0.54%
Mean economic cost for patients with RDs	70,510.43	61,476.73	69,654.07	83,791.29	66,563.93	-5.60%	-1.40%
Mean economic cost for patients with GHD	1,137.06	1,904.31	1,979.55	1,114.01	7,335.12	545.09%	136.27%
Mean economic cost for patients with TM	12,905.64	7,338.56	6,919.75	10,507.04	7,445.68	-42.31%	-10.58%
Mean economic cost for patients with HP	7,879.92	3,815.68	6,446.97	12,366.56	6,119.24	-22.34%	-5.59%
Mean economic cost for patients with NMO	5,231.54	7,247.72	8,747.90	9,120.13	4,179.05	-20.12%	-5.03%
Mean economic cost for patients with PG	2,654.36	2,103.42	3,831.33	3,514.04	6,070.19	128.69%	32.17%
Mean economic cost for patients with AAV	7,746.54	8,656.59	8,841.56	9,450.20	8,376.19	8.13%	2.03%
Mean economic cost for patients with PD	5,384.10	3,912.18	4,662.15	8,223.08	10,006.40	85.85%	21.46%
Mean economic cost for patients with AIE	17,969.23	14,569.45	18,052.19	18,886.25	4,446.58	-75.25%	-18.81%
Mean economic cost for patients with MS	4,449.71	5,856.59	6,197.80	4,898.03	9,164.97	105.97%	26.49%
Mean economic cost for patients with BD	5,152.33	6,072.22	3,974.88	5,711.96	3,420.51	-33.61%	-8.40%

Table 4. Annual estimated economic cost for patients with rare diseases in Hainan (US$)*. Notes: Percentage of economic cost= economic cost for each rare disease/total economic cost*100. Average economic cost= economic cost for patients with rare diseases/number of patients with rare diseases. Growth rate= (the value in 2023-the value in 2019)/the value in 2019. RDs: Rare diseases; GHD: Growth hormone deficiency; TM: Thalassemia major; HP: Haemophilia; NMO: Neuromyelitis optica; BD: Behcet disease; AAV: ANCA-associated vasculitis; PG: Pemphigus; PD: Early-onset Parkinson's disease; AIE: Autoimmune encephalitis; MS: Multiple sclerosis; US$: United States Dollars. *Estimated cost for 10 RDs (Bank of China exchange rate: US$ 1=7.3078 Chinese yuan [CNY], as of 2025.02.07).

prevalence of GHD increased significantly from 0.44% in 2019 to 1.20% in 2023; thalassemia major showed a similar trend, which increased from 0.46% in 2019 to 0.96% in 2023. The accumulated total expenditure for these rare diseases is illustrated in Table 4, with an average estimated cost of 2,572,319.65 CNY (US$ 351,996.45). AIE demonstrated the highest total mean cost at 21.00%, followed by TM and AAV at 12.82% and 12.24%, respectively. Overall expenditure growth rates per year notably increased for pemphigus (PG), GHD, AAV, PD, and MS. While some rare diseases experienced fluctuation over the 5-year period. Of the 10 RDs, 23.80% of the total mean cost was incurred in 2022, followed by 20.03% in 2019 and 19.79% in 2021. The highest total economic cost per disease was TM, accounting for 19.05% of the total cost, followed by AIE (14.32%), haemophilia (14.03%), GHD (11.61%) and NMO (11.12%), and the total economic cost per year peaked in 2023. Conversely, the average total cost per disease was highest for AIE, representing 21%, followed by TM (12.82%), AAV (12.24%) and haemophilia (10.41%), and the average total economic cost per year was highest in 2022.

Discussion

The findings of this study revealed a significant increase in the number of patients diagnosed with rare diseases (RDs) in Hainan Province over the five-year period from 2019 to 2023. The most common rare diseases identified in this study were growth hormone deficiency (GHD), thalassemia major (TM), haemophilia, neuromyelitis optica (NMO), pemphigus (PG), systemic sclerosis (SS), ANCA-associated vasculitis (AAV),

early-onset Parkinson's disease (PD), autoimmune encephalitis (AIE), myasthenia gravis (MG), polycythemia vera (PV), multiple sclerosis (MS), Behcet disease (BD), adult-onset Still disease and neurofibromatosis (NF). The economic costs of these rare diseases in Hainan Province were substantial, with the total annual economic cost increasing from 34.26 million CNY (US$ 4.69 million) in 2019 to 64.74 million CNY (US$8.86 million) in 2023, with hospitalisation costs and out-of-pocket expenses experiencing significant growth. This represents an annual growth rate of 88.99%, which is higher than the national average growth rate of health expenditures in China[17]. This also aligns with global trends showing that RDs often result in high medical expenditures due to the necessity for specialised treatments and long-term care[16,18,19]. Despite insurance coverage, out-of-pocket expenses remain a significant burden, emphasising the need for enhanced financial support systems for RD patients[10,20].

The total number of RD patients rose from 760 in 2019 to 1,328 in 2023, reflecting an increased recognition and diagnosis of rare diseases. This trend aligns with global studies reporting rising RD incidence due to advancements in diagnostic technologies and heightened awareness among healthcare providers[21–23]. Factors contributing to the increased diagnosis rates include improved diagnostic technologies such as genetic testing, and early screening modalities, which have enabled more accurate and timely diagnoses[24,25]; incentives for early diagnosis, including expanded insurance coverage for initial diagnostic tests, may have inflated the diagnosis rates of patients with rare disease[26,27]; and urbanisation and enhanced access to tertiary care centres have facilitated better detection and management of RDs. However, external variables, such as the COVID-19 pandemic, may have delayed earlier diagnoses, causing a shift in reporting to more recent periods[28,29]. Thus, the observed increase in diagnosis rates, from 760 patients in 2019 to 1,328 in 2023, may not solely reflect a rise in disease prevalence but could also be attributed to improved diagnostic capabilities, heightened awareness among healthcare providers, and changes in healthcare-seeking behaviour.

The average age at admission decreased from 37.18 years in 2019 to 27.46 years in 2023, suggesting that younger populations are increasingly being diagnosed, potentially due to improved diagnostic capabilities and heightened awareness among healthcare providers, such as early screening modalities[24,25]. Those below 9 years constituted 24.6% and 14.6% of the 10–19 years old of the total population. Similarly, students constituted 16.7% of the total population. The growing prevalence of RDs among children underscores the need for paediatric-focused management strategies, including tailored interventions and specialised resources[30]. The sharp rise in costs shown in this study can be attributed to multiple factors, including an increase in the number of patients diagnosed with RDs, rising hospitalisation costs, higher out-of-pocket expenses and the growing number of patients incurring expenses exceeding 20,000 CNY (US$2,736.80) per admission. The economic burden findings in this study are consistent with existing literature that demonstrates the high costs associated with managing rare diseases. Studies like those by Angelis et al. have shown that rare diseases often incur significant costs due to their chronic nature, the need for specialised treatments, and the frequent occurrence of comorbidities[15].

Rare diseases in China impose a significant economic burden on patients and their families, with high out-of-pocket (OOP) expenses and limited healthcare coverage[4,10,31]. The costs are exceptionally high for advanced therapies and long-term care[27], and the reported national OOP expenses in China accounted for 28% in 2020[32]. For instance, Lin et al. reported high OOP expenses across various age groups in patients with phenylketonuria (PKU)[33], while another study reported an estimated OOP mean cost of $1651 for PKU patients[34]. Additionally, research on amyotrophic lateral sclerosis (ALS) indicates an annual direct medical cost of 28,139.8 RMB per patient, with out-of-pocket expenses comprising 41.7% of the total cost[31]. The monthly OOP expenses for the treatment of thalassemia major in Pakistan were estimated at $500[35]. The annual mean OOP expenses for epidermolysis bullosa (EB) was €4129[36]. Consistently, our results demonstrated high OOP expenses for patients diagnosed with RDs, which showed an overall increment over the 5-year period, from 16.29% in 2019 to 17.32% in 2023; the highest was in 2022, accounting for 19.07% of the total annual cost. The rise in out-of-pocket expenses, which grew by 102.63% from 2019 to 2023, is particularly concerning, as it highlights the financial strain on patients and their families. This trend suggests that despite the availability of insurance, many patients still face significant financial barriers to accessing care.

The total cost of hospitalisation was the most significant component of the total economic cost, accounting for 49.16% of the total mean medical expenditure across the 5-year period. This finding aligns with previous studies, which have consistently shown that hospitalisation costs impose a substantial financial burden on patients with rare diseases[37–39]. The high proportion of hospitalisation total expenses underscores the reliance on resource-intensive inpatient care for managing rare diseases. For instance, individuals with thalassemia major require frequent blood transfusions and continuous monitoring, resulting in yearly hospital stays[40,41]. These admissions are often prolonged due to complications, further increasing total expenses. Secondly, the care provided during hospitalisations is typically intensive, involving specialised interventions and continuous monitoring. There are also ancillary costs, including laboratory tests, medications administered during the stay, and rehabilitation services following discharge[41,42]. This disproportionate financial burden associated with hospitalisation underscores the urgent need for expanded insurance reimbursements to comprehensively cover inpatient care.

The study also highlighted an increase in the use of antibiotics among RD patients, a finding consistent with recent studies on patients with spinal muscular atrophy (SMA)[43]. This rise in antibiotic use, alongside higher drug costs—particularly for Western medicine—further strains the financial resources of patients and their families. The financial impact is especially pronounced in resource-limited areas, where access to affordable medications remains a challenge[12]. The high costs of hospitalisation and medications mirror findings from other regions, underscoring the global nature of these challenges[37–39]. The significant contribution of these factors to the total economic burden emphasises the need for systemic reforms to improve healthcare affordability and access for RD patients worldwide.

As mentioned above, the 88.99% growth in rare disease-related costs over five years significantly surpasses the observed general healthcare expenditures in Hainan during the same period[12,13]. This stark contrast underscores the significant financial burden of rare diseases on the healthcare system. Furthermore, the average per-patient cost of managing rare diseases was estimated at 237,046.30 CNY (US$ 32,437.44) in 2023, which is higher than the average per capita healthcare expenditure in China, which stood at 2,460 CNY (US$336.63) in 2023[44]. These comparisons underscore the substantial economic burden attributed to rare diseases, highlighting the urgent need for policy reforms and broadened insurance coverage to address this imbalance effectively.

In contrast to the rising costs of hospitalisation and drug treatments, diagnostic costs remained relatively stable, accounting for 11.27% of total expenses over the five-year study period. This stability can be attributed to the consistency of established diagnostic protocols, which have minimised cost variability. While high upfront costs are associated with technologies such as genetic sequencing, their widespread adoption has effectively reduced per-test costs over time[10]. Moreover, subsidies for diagnostic tests, particularly those aimed at early detection programmes, have helped maintain stable diagnostic costs, reflecting the success of policies that prioritise early diagnosis. Investments in diagnostic technologies should focus on expanding access in underserved regions, ensuring equitable healthcare delivery for rare disease patients across diverse demographics.

The present study also found that the proportion of costs covered by insurance declined from 34.69% in 2019 to 30.60% in 2023, while out-of-pocket (OOP) expenditures increased from 16.29 to 17.32% during the same period. Uninsured RD patients accounted for 16.99% of the total population, further emphasising the growing financial burden on patients and their families. This trend is concerning, as OOP expenses disproportionately affect low-income households, exacerbating financial hardship for those with limited resources[31]. This decline can be attributed to several key factors, including shifting priorities in health insurance schemes such as URBMI, rising healthcare costs that have not been adequately addressed by insurance adjustments, and limited coverage for high-cost treatments due to administrative hurdles[45–47]. This trend is consistent with findings from other regions, where underfunded schemes disproportionately impact vulnerable populations[48]. These adjustments or economic challenges limit insurance coverage, further exacerbating financial vulnerability, particularly for patients with rare diseases, who often require resource-intensive care.

Selected individual RDs with high economic costs included autoimmune encephalitis (AIE), which accounted for the highest total mean cost, followed by thalassemia major, anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), haemophilia and neuromyelitis optica (NMO). These conditions often require intensive and long-term treatments, significantly contributing to their high financial burdens. Although thalassemia major represents only 9.34% of the total studied population, it incurred the highest economic cost, accounting for 19.07% of the total cost compared to growth hormone deficiency (GHD). This aligns with previous studies due to its associated transfusion-related cost, which adds financial strain on patients and family members. For example, Zhen et al. reported an annual cost of $2,764 per patient for thalassemia major (TM)[41], while another study estimated costs at $981 per patient per year[40]. Udeze et al. estimated the lifetime healthcare cost for TM patients to be $7.1 million, with an annual expenditure of $137,125[49]. AIE also showed a similar trend, probably due to its diagnostic complexity and limited available treatment options, in accordance with prior studies[50]. The economic burden of haemophilia also remains substantial. For instance, the total mean cost for managing haemophilia in Belgian patients was estimated to be €97,336,761[51].

Healthcare insurance serves as a critical safeguard for patients with rare diseases (RDs). However, affordable and accessible treatment remains a significant challenge, as many healthcare insurance schemes in China offer limited coverage for RDs, particularly for those with high diagnostic costs[52]. The present study revealed significant variability in insurance coverage for RD patients in Hainan Province. The most common insurance type was Urban and Rural Resident Basic Medical Insurance (URBMI), covering 38.33% of patients, followed by Urban Employee Basic Medical Insurance (UEBMI) and New Rural Cooperative Medical Insurance (NRCMI). The predominance of URBMI, covering 38.33% of patients, reflects the demographic and socioeconomic shifts in Hainan Province. As urbanisation accelerates, many rural residents transition to urban insurance schemes like URBMI, which offer broad coverage at subsidised premiums[10,53]. Despite its popularity, URBMI offers limited coverage for high-cost treatments and orphan drugs. In contrast, UEBMI showed a declining trend, dropping from 16.53 to 12.77%. This decline may be attributed to structural shifts in workforce demographics and changes in employer-based insurance policies. Meanwhile, NRCMI exhibited relatively stable but low coverage rates, indicating limited adoption in rural and private sectors. The slight increase in poverty relief health insurance users suggests that economic disparities continue to affect RD patients[47]. However, the study in Hainan Province highlights a slightly lower proportion of costs covered by insurance compared to some studies from high-income countries, where insurance coverage for rare diseases might be more comprehensive. For instance, research in Europe suggests that while rare diseases are costly, extensive insurance coverage helps mitigate out-of-pocket expenses for patients[54,55]and in the US[8,38], a factor that seems less pronounced in Hainan, though the country as a whole made positive strides in healthcare insurance coverage[48]. This suggests a potential gap in the insurance coverage for rare diseases in Hainan, which might be addressed through policy improvements.

This study underscores the substantial economic burden that RDs impose on patients and the healthcare system in Hainan Province. The increasing diagnosis rates and associated costs underscore the urgency for policy interventions to expand insurance coverage and develop comprehensive support systems for RD patients[27,48]. Our findings also highlight the need for more comprehensive and affordable health insurance coverage for patients with rare diseases. This is particularly important in China, where the healthcare system is undergoing significant reforms aimed at improving healthcare financing and access to healthcare services[24,46]. The Chinese government has introduced various policies to improve healthcare financing, including the establishment of a national health insurance system and the introduction of a catastrophic illness insurance system[45,56]. However, more comprehensive and affordable healthcare services for RD patients are essential to ensure equitable access and alleviate financial burdens.

Strengths and weaknesses

The variation in patient numbers and economic costs associated with different rare diseases over the study years can be attributed to several analytical factors, including disease prevalence, medical advances, healthcare policies, the complexity of management, and socio-economic considerations.

Some rare diseases may have seen a spike in patient numbers due to increased awareness and improved diagnostic capabilities. For example, healthcare providers might have become more familiar with the symptoms of certain diseases, leading to more diagnoses. Furthermore, increased awareness of preventive measures for certain rare diseases and counselling for genetic-related rare diseases might also significantly influence rare disease prevalence and economic cost variability. Technological advancements, such as improved genetic testing or imaging techniques, could also have contributed to a rise in identified cases in specific years. Some diseases are associated with lifestyle factors or comorbid conditions that enhance the overall healthcare burden[24,25].

Epidemiological changes, such as during the COVID-19 pandemic, which limited people's movement to seek medical attention due to the policies implemented to curtail the disease, might have influenced the prevalence of certain rare diseases in particular years, as observed in our present study. The pandemic significantly disrupted healthcare access, leading to delayed diagnoses of rare diseases in 2020. Patients with rare respiratory conditions, notably ANCA-associated vasculitis (AAV), experienced delays in diagnoses due to symptom overlap with COVID-19, including respiratory distress, fever, and fatigue[29,57]. Furthermore, the reallocation of resources during peak pandemic phases—such as intensive care unit (ICU) beds and healthcare personnel—significantly curtailed diagnostic opportunities for non-urgent cases[58,59]. Empirical studies have indicated a decline in new diagnoses of rare respiratory diseases throughout 2020, succeeded by a compensatory rise in 2021 as healthcare systems began to recover[60,61](Hampson C, 2022; Chiner-Vives E, 2022). Subsequently, a compensatory rise in diagnoses occurred as postponed cases were addressed in later years[28,62]. In addition, Heightened awareness of healthcare systems during the pandemic prompted individuals to seek evaluations for previously undiagnosed conditions once restrictions were lifted. However, the pandemic amplified disparities in healthcare access, with rural areas facing more significant delays compared to urban centres[10,63]. This trend elucidates the dual impact of the pandemic, characterised by initial diagnostic delays followed by subsequent surges in diagnoses. Another instance, a rise in cases of autoimmune diseases could be linked to environmental triggers or changes in population behaviour that exposed more individuals to risk factors.

Some rare diseases are inherently more complex and chronic, requiring long-term care, repeated hospitalisations, and expensive treatments. Conditions like thalassemia major (TM) and autoimmune encephalitis (AIE) often necessitate lifelong management, including frequent blood transfusions, chelation therapy, or immunosuppressive treatments, which significantly drive up healthcare costs[49]. The economic burden of a rare disease is often closely linked to the cost of its treatment. Diseases that require expensive medications, such as biologics for autoimmune conditions or enzyme replacement therapies for metabolic disorders, will naturally have higher associated costs. The cost of novel therapies, such as gene therapy, which might be available only for certain conditions, can also be a significant contributing factor. The extent of insurance coverage also plays a role in the economic burden of rare diseases. Diseases that are less likely to be fully covered by insurance or that involve treatments not included in standard insurance plans might result in higher out-of-pocket costs for patients, thereby increasing the perceived economic burden. Diseases frequently resulting in hospitalisation, particularly in intensive care units, can have a higher economic cost due to the high daily costs of inpatient care. Conditions like AIE, which may require prolonged hospital stays and intensive care, will incur substantial costs[64].

Limitations

The study involved a limited number of patients due to the rarity of the diseases, which can affect the generalisability of the findings to the broader population of Hainan or other regions. Secondly, the studied population may not represent all demographics or socioeconomic statuses, as outpatient costs for rare disease patients, indirect costs and non-medical costs were not assessed in this study, leading to biased results that do not fully capture the economic burden across diverse groups. Third, rare diseases vary widely in their nature and required treatments, making it difficult to generalise economic costs across different conditions. Also, the cost of medical services and treatments can vary significantly between urban and rural areas, leading to variability in the reported economic burden. Despite these limitations, this study provided valuable insights into the economic burden of rare diseases in Hainan province that will inform healthcare policy and resource allocation decisions.

Conclusion

In conclusion, this study provides valuable insights into the prevalence and economic burden of rare diseases in Hainan Province. The results suggest that there is a significant need for more comprehensive and affordable health insurance coverage for patients with rare diseases. The study's findings also highlight the need to develop targeted interventions and treatment strategies to reduce the economic burden of rare diseases and provide an in-depth framework for future studies on the economic burden of rare diseases in other regions or countries. Further research is needed to better understand the healthcare needs and experiences of patients with rare diseases in Hainan Province and China and to inform policy initiatives to improve healthcare financing and access to healthcare services.

Data availability

All data generated or analysed during this study are included in this published article.

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Author contributions

J L, LD and JSD conceptualized and designed the manuscript; XC, LD and JSD data retrieval and initial analysis; and JSD, JL and BA critically reviewed and revised the manuscript. All the authors approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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